The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease

The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease[1–4]

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ABSTRACT

Background: Low-grade systemic inflammation, particularly elevated IL-6, predicts mortality in chronic obstructive pulmonary disease (COPD). Although altered body composition, especially increased visceral fat (VF) mass, could be a significant contributor to low-grade systemic inflammation, this remains unexplored in COPD.

Objective: The objective was to investigate COPD-specific effects on VF and plasma adipocytokines and their predictive value for mortality.

Design: Within the Health, Aging, and Body Composition (Health ABC) Study, an observational study in community-dwelling older persons, we used propensity scores to match $n = 729$ persons with normal lung function to $n = 243$ persons with obstructive lung disease (OLD; defined as the ratio of forced expiratory volume in 1 s to forced vital capacity $<$ lower limit of normal). Matching was based on age, sex, race, clinic site, BMI, and smoking status. Within this well-balanced match, we compared computed tomography–acquired visceral fat area (VFA) and plasma adipocytokines, analyzed independent associations of VFA and OLD status on plasma adipocytokines, and studied their predictive value for 9.4-y mortality.

Results: Whereas whole-body fat mass was comparable between groups, persons with OLD had increased VFA and higher plasma IL-6, adiponectin, and plasminogen activator inhibitor 1 (PAI-1). Both OLD status and VFA were independently positively associated with IL-6. Adiponectin was positively associated with OLD status but negatively associated with VFA. PAI-1 was no longer associated with OLD status after VFA was accounted for. Participants with OLD had increased risk of all-cause, respiratory, and cardiovascular mortality, of which IL-6 was identified as an independent predictor.

Conclusion: Our data suggest that excessive abdominal visceral fat contributes to increased plasma IL-6, which, in turn, is strongly associated with all-cause and cause-specific mortality in older persons with OLD. *Am J Clin Nutr* 2012;96:516–26.

INTRODUCTION

In older adults, the prevalence of chronic obstructive pulmonary disease (COPD)[5] is 14%, and as a consequence of general aging in the population and improved medical intervention, this prevalence is projected to increase even further (1). COPD is characterized by altered body composition toward a relative or absolute increase in fat mass, low-grade systemic inflammation, and high mortality (2). Classically, low-grade systemic inflammation in these patients has been considered to be the result of a "spillover" of inflammatory mediators from the inflamed pulmonary compartment. For this, however, there has been no convincing evidence during clinically stable disease. The possibility of extrapulmonary tissues contributing to low-grade systemic inflammation in COPD has been relatively unexplored.

Adipose tissue has emerged as a potent producer of mediators of inflammation and energy homeostasis, termed *adipocytokines* (3), including IL-6, plasminogen activator inhibitor 1 (PAI-1), leptin, and adiponectin. Notably, in diseases associated with

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[5] Abbreviations used: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Health ABC, Health, Aging, and Body Composition; HEI, Healthy Eating Index; LLN, lower limit of normal; OLD, obstructive lung disease; PAI-1, plasminogen activator inhibitor 1; SF, subcutaneous fat; VF, visceral fat; VFA, visceral fat area.

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excessive fat mass, such as obesity and type 2 diabetes, adipose tissue has been suggested to be the source of low-grade systemic inflammation (4). In a recent clinical study, we examined adipocytokine gene expression and macrophage markers in biopsies from the abdominal subcutaneous fat (SF) compartment from COPD patients and fat mass–matched healthy subjects (5). We found positive associations between fat mass and adipose tissue inflammation, which were highly comparable between COPD patients and controls. These data suggested that the SF compartment may not be the primary fat compartment contributing to low-grade systemic inflammation in COPD. Importantly, studies consistently indicate that the inflammatory capacity of abdominal visceral fat (VF) is considerably greater in comparison with other fat depots that include SF (6, 7). Thus, VF may be a more plausible source of systemic inflammation than SF. Interestingly, a recent study in normal-weight patients with mild-to-moderate COPD and healthy subjects used abdominal computed tomography scanning and found increased VF area (VFA) in COPD patients (8). However, these patients also had increased whole-body fat mass, and it is unclear whether the increased VF was a reflection of the higher whole-body fat mass. Also, associations between VF and circulating adipocytokines were not assessed.

Whole-body fat mass increases with aging, and data have consistently shown that in this process, the expansion rate of VF exceeds that of SF (9, 10). Recently, in a review of inflammatory markers in population studies of aging, it has been proposed that aging-related mortality is associated with VF accumulation and "inflammaging" (11). Collectively, these studies stress the need for investigating the role of VF in low-grade systemic inflammation and mortality in COPD while accounting for important confounders including age and BMI. The current study provides a comprehensive comparison of VF mass and plasma adipocytokines and their relation with 9.4-y mortality in COPD patients and propensity score–matched persons with normal lung function who participated in the Health, Aging, and Body Composition (Health ABC) Study. In addition, we explored dietary intake and physical activity as important lifestyle determinants in these subjects.

SUBJECTS AND METHODS

Study population

The observational Health ABC Study included 3075 community-dwelling black and white men and women between the ages of 70 and 79 y residing in and near Pittsburgh, PA, and Memphis, TN. Baseline data were obtained in 1997–1998 through in-person interviews and clinic-based examinations. Inclusion criteria were as follows: no self-reported difficulty walking a quarter of a mile, climbing 10 steps without resting, or performing mobility-related activities of daily living. Exclusion criteria were any life-threatening condition, participation in any research study involving medications or modification of eating or exercise habits, plans to move from the geographic area within 3 y, and difficulty in communicating with the study personnel or cognitive impairment. The study was approved by the institutional review boards of the participating centers—University of Tennessee Health Science Center, Memphis (approval no. 95-05531-FB) and the University of Pittsburgh (approval no. 960212)—and of the coordinating center at the University of California, San Francisco (approval no. 10-03322). Written informed consent was obtained for all participants. Clinic site, age, and race (black or white) were based on self-report. In the current study we retrospectively analyzed baseline phenotypical data and 9.4-y mortality data.

Lung function and smoking history

Prebronchodilator lung function was assessed according to international standards as previously reported (12). Because postbronchodilator lung function was lacking, participants with a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) below the age, sex, and race-normalized lower limit of normal (LLN) (12–14) were regarded as having obstructive lung disease (OLD). This method is the same as that used in previous publications from the Health ABC Study (12, 15). Participants with restrictive lung disease ($FEV_1/FVC \geq$ LLN but $FVC <$ LLN) were excluded (**Figure 1**). Normal lung function was defined as $FEV_1/FVC \geq$ LLN and $FVC \geq$ LLN. Participants with missing lung function and those with noninterpretable lung function measurements according to international criteria were excluded. Cigarette smoking status (current, former, or never) and the number of pack-years smoked (1 pack-year = 20 cigarettes/d for 1 y) were obtained on the basis of self-report.

Anthropometric and body composition measurements

Height was measured by using a wall-mounted stadiometer. Body weight was assessed to the nearest 0.1 kg by using a standard balance beam scale, and BMI was calculated as weight/height squared (kg/m^2). Whole-body dual-energy X-ray absorptiometry (Hologic 4500A software version 8.21; Hologic) was used to assess total fat and fat-free masses.

Abdominal computed tomography

At 120 kVp and 200–250 mA a 10-mm computed tomography scan of the abdomen was acquired at the L4–L5 level. Subjects were placed in the supine position with their arms above their head and legs elevated with a cushion to reduce the curve in the back. In Memphis the scan was acquired by using a Somatom Plus 4 (Siemens) or a Picker PQ 2000S (Marconi Medical Systems), and in Pittsburgh the scan was acquired by using a 9800 Advantage (General Electric). VFA was manually distinguished from SF area by tracing along the fascial plane defining the internal abdominal wall. Areas were calculated by multiplying the number of pixels of a given tissue by the pixel area (*see* reference 16 for further details).

Circulating adipocytokines

IL-6, PAI-1, TNF-α, C-reactive protein, leptin, and adiponectin were obtained from frozen, stored plasma or serum obtained from a venipuncture after an overnight fast [a detailed description of measurement techniques was previously published (17)].

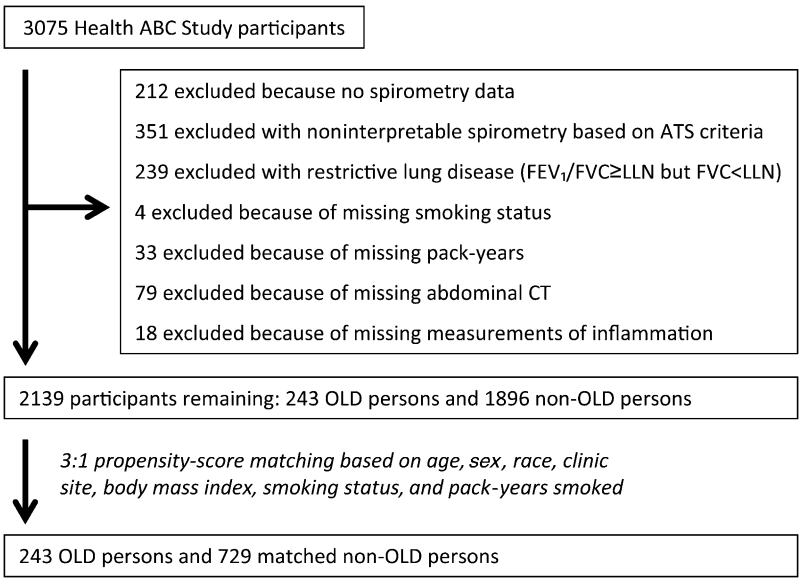

FIGURE 1. Flow diagram of selection of study participants. ATS, American Thoracic Society; CT, computed tomography scan; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Health ABC Study, Health, Aging, and Body Composition Study; LLN, lower limit of normal; OLD, obstructive lung disease.

Insulin resistance

HOMA-IR was used to estimate insulin resistance according to the formula (fasting plasma glucose × fasting plasma insulin)/22.5 (18).

Prevalent diseases

The metabolic syndrome was defined according to international guidelines (19) as meeting ≥3 of the following criteria: *1*) waist circumference ≥102 cm in men and ≥88 cm in women, *2*) diastolic blood pressure ≥85 mm Hg and/or systolic blood pressure ≥130 mm Hg or use of antihypertensive medications, *3*) fasting glucose concentration ≥100 mg/dL or use of antidiabetic medication, *4*) HDL cholesterol concentration <40 mg/dL in men and <50 mg/dL in women or currently receiving treatment for low HDL cholesterol, and *5*) serum triglyceride concentration ≥150 mg/dL or currently receiving drug treatment for high triglycerides. Diabetes was defined by self-report or the use of diabetes medication. Cardiovascular disease was defined by self-report or by medical records of coronary heart disease and/or stroke. Two seated resting blood pressure measurements were taken and were averaged. Physiologic hypertension was defined by systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or use of hypertension medication.

Survival time and cause of death

Surveillance for survival was conducted by in-person visits alternating with telephone interviews every 6 mo. The date of death was determined on the basis of hospital records, death certificates, or informant interviews. Thirty-eight persons (3%) were lost during follow-up, and their survival time was censored on the basis of their date of last contact. Deaths were adjudicated by a central committee for immediate and underlying causes of death by using established criteria, including review of death certificate, all recent hospital records, and interview with the next of kin. Respiratory mortality was defined as mortality from COPD, pneumonia, and respiratory failure. We defined cardiovascular mortality as mortality from atherosclerotic cardiovascular disease (definite fatal myocardial infarction or definite or possible fatal coronary heart disease), stroke, atherosclerotic disease other than coronary or cardiovascular, and other cardiovascular disease.

Dietary intake and physical activity level

Usual nutrient and food group intake was estimated by administering a modified Block food-frequency questionnaire by a trained dietary interviewer at the first annual follow-up examination (details published in reference 20). A Healthy Eating Index (HEI) was calculated to measure the amount of variety in the diet and compliance with specific dietary guidelines (20). HEI scores ranged from 0 to 100, with higher scores indicating better compliance with the recommended intake range or amount. Physical activity level was assessed at baseline by means of a validated questionnaire (20).

Statistical analyses

Propensity-score matching

After exclusion criteria were applied, n = 2139 participants (n = 243 persons with OLD and n = 1896 persons without OLD) were identified (Figure 1). By means of independent t tests, Mann-Whitney U tests, and chi-square tests as appropriate, sex, age, BMI, pack-years smoked, and smoking status were found to be significantly different between persons with and without OLD (**Table 1**). To enable balanced comparisons between persons with and without OLD by accounting for these confounders, we performed propensity-score matching (21). For this, propensity scores for OLD status were calculated for the entire population (n = 2139) by using logistic linear regression on the

TABLE 1
Sociodemographic data before and after propensity-score matching[1]

		Before matching		After matching	
	OLD participants (n = 243)	Non-OLD participants (n = 1896)	Standardized difference	Non-OLD participants (n = 729)[2]	Standardized difference
			%		%
Sex (% men)	58	47**	22.8	58	0.0
Age (y)	73 ± 3[3]	74 ± 3*	19.9	73 ± 3	0.2
Race (% white)	54	61	13.9	56	2.8
Clinic site (% Memphis)	51	46	9.2	48	1.5
BMI (kg/m^2)	25.6 ± 4.6	27.4 ± 4.5**	40.6	25.7 ± 4.1	4.1
Pack-years smoked	38 (9, 57)[4]	2 (0, 25)**	84.5	30 (6, 63)	3.3
Smoking status (%)					
Current smoker	27.6	7.8**	66.0	18.6	22.4
Former smoker	54.7	44.5**	20.5	61.6	14.1
Never smoker	17.7	47.7**	60.4	19.9	5.6

[1] *,**Significant difference compared with OLD participants as tested by independent t tests, Mann-Whitney U tests, and chi-square tests as appropriate: *$P < 0.01$, **$P < 0.001$. OLD, obstructive lung disease.
[2] No significant difference compared with OLD participants for any of the variables as tested with random-effects ANOVA.
[3] Mean ± SD (all such values).
[4] Median; IQR in parentheses (all such values).

basis of sex, age, race, clinic site, BMI, smoking status, and pack-years smoked. Subsequently, 3 non-OLD participants were matched to each OLD person with the closest propensity score. In this procedure we allowed for replacement of non-OLD persons, which has been shown to increase balance (22).

Four methods were used to assess the success of matching. First, we confirmed that none of the variables included in the propensity-score calculation was statistically different between persons with and without OLD after matching (Table 1), indicating that a balanced match was reached. Also, comparisons of the mean propensity scores between persons with and without OLD before (0.211 ± 0.149 compared with 0.101 ± 0.093; $P < 0.001$) and after (0.211 ± 0.149 compared with 0.211 ± 0.149; $P = 0.99$) matching showed a perfect match. In addition, the standardized differences between persons with and without OLD for the variables included in the propensity-score calculation were compared before and after matching (Table 1). The standardized differences were calculated as the absolute difference in sample means divided by the SD of the total population and expressed as a percentage (23). The standardized differences were considerably improved by the matching and reached acceptable levels. Finally, empirical quantile-quantile plots were created before and after matching for the continuous variables included in the propensity-score calculation (ie, age, BMI, and pack-years). These plots allowed for a visual inspection of the data distribution in persons with and without OLD and showed that the equality of data distribution was markedly improved by the matching procedure (**Figure 2**).

Analyses within the established match

It is crucial that comparisons made after propensity-score matching account for the lack of independence between matched sets (23). We used random-effects ANOVA to test phenotypical differences between persons with and without OLD. Association analyses were performed by using linear mixed models in which matched sets were treated as random factors. Cox proportional hazards models that accounted for correlated data (24) were performed to investigate the HR of all-cause, respiratory, and cardiovascular mortality of persons with OLD relative to matched non-OLD participants. These models were first performed unadjusted and adjusted for the variables included in the propensity-score calculation. Subsequently, the phenotypical variables that were significantly different between OLD and matched non-OLD participants were added to the model to test whether these predicted mortality and modified mortality by OLD status.

R version 2.11.1 (R Project for Statistical Computing) was used to establish the match (Matching package), to perform the linear mixed models (nlme package), and to perform the proportional hazards models (Survival package). Random-effects ANOVAs were performed in Predictive Analytics SoftWare Statistics 17.0 (SPSS Inc).

RESULTS

Phenotypical differences between OLD and matched non-OLD persons

The main phenotypical characteristics of persons with OLD and matched non-OLD participants are summarized in **Table 2**. At the whole-body level, fat and fat-free masses were not different. Yet, OLD persons had significantly greater VFA ($P < 0.001$) although SF area did not differ. Circulating concentrations of IL-6, adiponectin, and PAI-1 were significantly higher in OLD persons, whereas concentrations of C-reactive protein, TNF-α, and leptin were not different. Apart from a higher prevalence of hypertension in persons with OLD, no differences were found for the HOMA-IR, diabetes and cardiovascular disease prevalence, or metabolic syndrome criteria.

Association analyses

Our findings of concomitantly increased VFA, IL-6, adiponectin, and PAI-1 suggest that VF may be a significant contributor to these elevated circulating adipocytokines. The data from the linear mixed-effects models that analyzed the independent

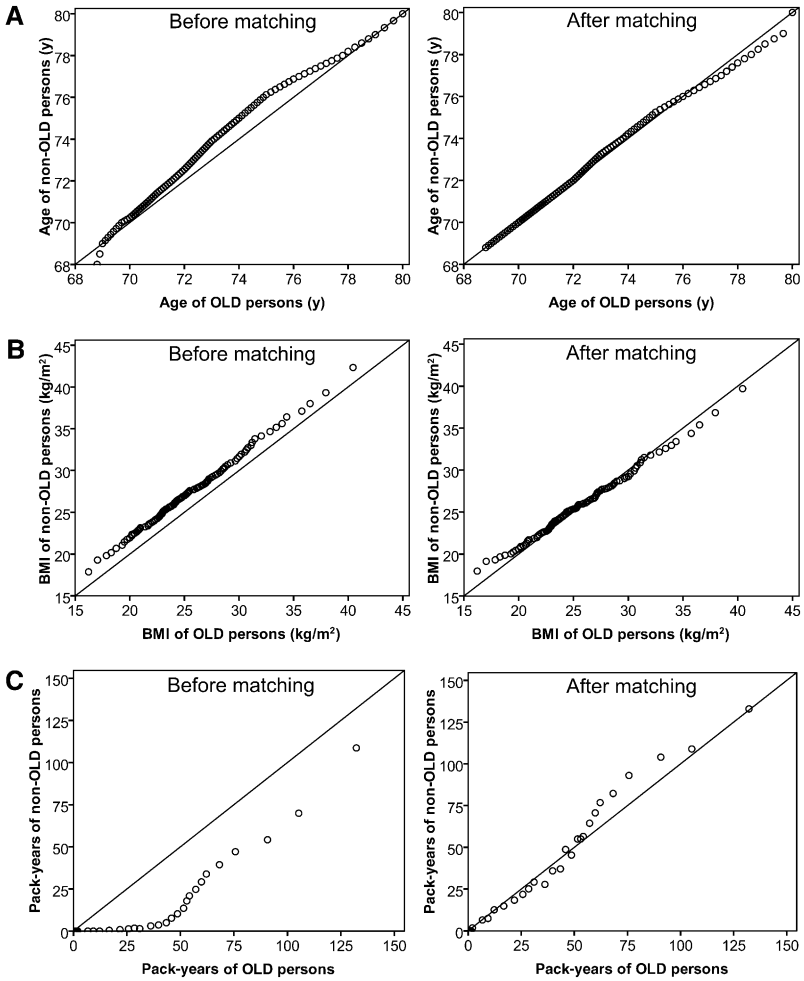

FIGURE 2. Empirical quantile-quantile plots for age (A), BMI (B), and pack-years smoked (C) before and after matching. Quantiles of age, BMI, and pack-years smoked for OLD and non-OLD participants were plotted against each other before and after matching. The solid line indicates $y = x$, which represents the situation in which the 2 distributions being compared are equal. It can be observed that the matching improved balance considerably. The "Before matching" panels describe data from $n = 243$ OLD participants and $n = 1896$ non-OLD participants, and the "After matching" panels describe data from $n = 243$ OLD participants and $n = 729$ non-OLD participants. OLD, obstructive lung disease.

associations of VFA and OLD status on these plasma adipocytokine concentrations are summarized in **Table 3**. VFA and OLD status were both significantly and independently associated with IL-6. OLD status was positively associated with adiponectin, independently of VFA, and VFA was negatively associated with adiponectin. OLD status was no longer associated with PAI-1 after VFA, which was significantly associated with PAI-1, was accounted for. The data from these models did not change after further adjustment for BMI, which suggests specific VF effects.

Mortality analyses

During a median follow-up period of 9.4 y (7728 person-years), 104 persons with OLD (43%) and 201 persons without OLD (28%) died of all causes. Unadjusted Cox proportional hazards models showed a significantly worse survival in persons with OLD compared with matched non-OLD participants for all-cause mortality (HR: 1.70; 95% CI: 1.29, 2.34; $P < 0.001$) (**Figure 3**A). As expected, respiratory mortality risk was significantly higher in persons with OLD (HR: 4.03; 95% CI: 2.12, 7.64; $P < 0.001$) (Figure 3B). In addition, cardiovascular mortality risk was significantly higher in persons with OLD (HR: 1.76; 95% CI: 1.07, 2.89; $P = 0.026$) (Figure 3C). The analyses of predictors for mortality are described in **Table 4**. Adjustment for the variables included in the propensity-score matching had no major effect on these HRs (model 2). Because we found increased VFA, higher hypertension prevalence, and elevated IL-6, adiponectin, and PAI-1 in persons with OLD compared with matched non-OLD participants, we studied whether these factors predicted mortality (model 3). IL-6 and adiponectin independently predicted all-cause mortality. In the final model, only IL-6 remained significant. IL-6 was also found to be a strong and independent predictor of respiratory and cardiovascular mortality. PAI-1, VFA, and hypertension were not predictors of mortality.

The primary and underlying causes of mortality in persons with OLD and matched non-OLD participants are summarized in **Table 5**. Primary respiratory and cardiovascular causes were particularly common in persons with OLD, whereas cardiovascular causes were most represented among non-OLD participants. Respiratory causes were reported as the underlying cause of mortality in 15% of persons with OLD and in only 3% in non-

TABLE 2
Phenotypical characteristics of OLD and matched non-OLD participants[1]

	OLD participants (n = 243)	Non-OLD participants (n = 729)	P value
Pulmonary function			
FEV_1 (% predicted)[2]	63 ± 18[3]	99 ± 16	<0.001
FVC (% predicted)[2]	81 ± 18	98 ± 14	<0.001
FEV_1/FVC (%)	57 ± 7	75 ± 5	<0.001
Body composition			
Weight (kg)	72.6 ± 14.9	72.3 ± 14.4	NS
Fat mass (kg)	23.9 ± 8.4	23.4 ± 7.2	NS
Fat-free mass (kg)	48.7 ± 10.5	49.0 ± 10.7	NS
Subcutaneous fat area (cm^2)	246 ± 118	238 ± 101	NS
Visceral fat area (cm^2)	143 ± 77	123 ± 59	<0.001
Systemic adipocytokines			
IL-6 (pg/mL)	2.16 (1.52, 3.34)[4]	1.75 (1.20, 2.69)	<0.001
CRP (μg/mL)	2.0 (1.2, 3.7)	1.4 (0.9, 2.6)	NS
TNF-α (pg/mL)	3.03 (2.35, 4.08)	3.10 (2.40, 4.07)	NS
PAI-1 (ng/mL)	22 (12, 37)	18 (11, 31)	0.008
Adiponectin (μg/mL)	12.3 ± 7.4	11.3 ± 6.7	0.037
Leptin (ng/mL)	7.61 (3.33, 14.07)	7.86 (4.22, 14.28)	NS
Insulin sensitivity			
HOMA-IR	1.5 (1.1, 2.3)	1.5 (1.0, 2.2)	NS
Metabolic syndrome (%)			
Abdominal obesity	48	45	NS
High blood pressure	79	77	NS
High glucose	21	20	NS
Low HDL	24	26	NS
High triglycerides	21	20	NS
Prevalent diseases (%)			
Hypertension	66	56	0.010
Diabetes	12	13	NS
Cardiovascular disease	22	28	NS

[1] Analyses were performed by using random-effects ANOVA. CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; OLD, obstructive lung disease; PAI-1, plasminogen activator inhibitor 1.
[2] Calculated from reference equations (13).
[3] Mean ± SD (all such values).
[4] Median; IQR in parentheses (all such values).

OLD participants, whereas cardiovascular causes underlying mortality were most common in non-OLD participants.

Dietary intake and physical activity level

As previously explained, pack-years smoked and smoking status were matched between the persons with and without OLD. Consequently, the current study population consisted of mainly current/former smokers with a relatively high number of pack-years.

Food-frequency questionnaire data were available for n = 210 OLD participants and n = 565 non-OLD participants (**Table 6**). Although total energy, total protein, and total carbohydrate intake were not different between the groups, persons with OLD had significantly higher intakes of total fat, saturated fat, cholesterol, and *trans* fat. Persons with OLD also had a significantly lower intake of dietary fiber, which was attributable to a lower amount of fiber from fruit and vegetables (data not shown). In addition, daily vitamin C intake was significantly lower in persons with OLD. Although daily glycemic load was not different, daily glycemic index was significantly higher in persons with OLD. On average, HEI scores were within the range that has been classified as "needs improvement" in persons with and without OLD, but these scores were even lower in OLD participants.

Total physical activity was significantly lower in OLD compared with non-OLD participants (Table 6). More specifically, fewer OLD participants walked briskly for ≥90 min/wk and fewer OLD participants performed high-intensity exercise for ≥90 min/wk compared with non-OLD participants.

DISCUSSION

We aimed to unravel OLD-specific effects from age-related effects on VF mass, to study the associations between VF and adipocytokines by OLD status, and to investigate their relation with mortality. We found that persons with OLD had significantly increased VF mass independent of age, BMI, and whole-body fat mass. Our data suggest that this excessive VF contributes to increased plasma IL-6, which was subsequently shown to be a strong predictor of all-cause, respiratory, and cardiovascular mortality. In addition, persons with OLD engaged in an unhealthier lifestyle that was characterized by poorer dietary quality and a lower daily physical activity level.

TABLE 3
Mixed-model analyses investigating the independent associations of OLD status and VFA on plasma concentrations of IL-6, adiponectin, and PAI-1[1]

	Model 1		Model 2		Model 3	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
IL-6 (log-transformed)						
OLD status						
Non-OLD	0 (reference)		0 (reference)		0 (reference)	
OLD	0.095 (0.019)	<0.001	0.081 (0.019)	<0.001	0.080 (0.020)	<0.001
VFA (dm^2)			0.063 (0.015)	<0.001	0.070 (0.019)	<0.001
Adiponectin (μg/mL)						
OLD status						
Non-OLD	0 (reference)		0 (reference)		0 (reference)	
OLD	1.04 (0.45)	0.022	1.93 (0.42)	<0.001	1.69 (0.43)	<0.001
VFA (dm^2)			−4.39 (0.30)	<0.001	−3.37 (0.40)	<0.001
PAI-1 (log-transformed)						
OLD status						
Non-OLD	0 (reference)		0 (reference)		0 (reference)	
OLD	0.068 (0.023)	0.004	0.021 (0.022)	NS	0.027 (0.022)	NS
VFA (dm^2)			0.222 (0.015)	<0.001	0.196 (0.021)	<0.001

[1] Analyses were performed by using linear mixed models. Model 1 was adjusted for age, sex, race, clinic site, smoking status, and pack-years smoked. Model 2 was adjusted as for model 1 plus adjustment for VFA. Model 3 was adjusted as for model 2 plus adjustment for BMI. OLD, obstructive lung disease; PAI-1, plasminogen activator inhibitor 1; VFA, visceral fat area.

Making use of the wealth of data in the Health ABC Study, we were able to carefully match a non-OLD control group to OLD participants by using propensity-score matching for important confounders. This approach allowed us to disentangle OLD-specific effects from age-related effects for body fat distribution, inflammation, and mortality. We found that a number of plasma adipocytokines were not different between OLD and matched non-OLD participants. It is possible that whole-body fat mass rather than specific VF may be implicated, and because whole-body fat mass was matched, no differences in these markers were observed.

Our results cannot be generalized to all older persons, especially those with severe OLD, because participants in the Health ABC Study were selected to be able to walk a quarter of a mile and to climb 10 steps without resting. Our data apply to an older population with OLD with, on average, mild airflow obstruction. A limitation in the Health ABC Study is that no postbronchodilator pulmonary function is available, which precludes the application of Global Initiative of Obstructive Lung Disease criteria for defining COPD. However, instead of using the same cutoffs for all individuals, we used stringent criteria based on age-, sex-, and race-adjusted LLN cutoffs to define OLD in this older and multiethnic population, as recommended by previous studies (25) and as used in earlier Health ABC Study publications (12, 14, 15).

Elevated plasma IL-6 has been consistently reported in COPD patients (26–30) and has recently been identified as an important biomarker with added predictive value for mortality in addition to clinical predictors (31). It is estimated that approximately one-third of plasma IL-6 originates from adipose tissue, and in obese subjects visceral adipocytes produce 3-fold the IL-6 as do subcutaneous adipocytes (7). Other potential sources may include "spillover" from the pulmonary compartment, but the liver, peripheral skeletal muscle, circulating immune cells, and

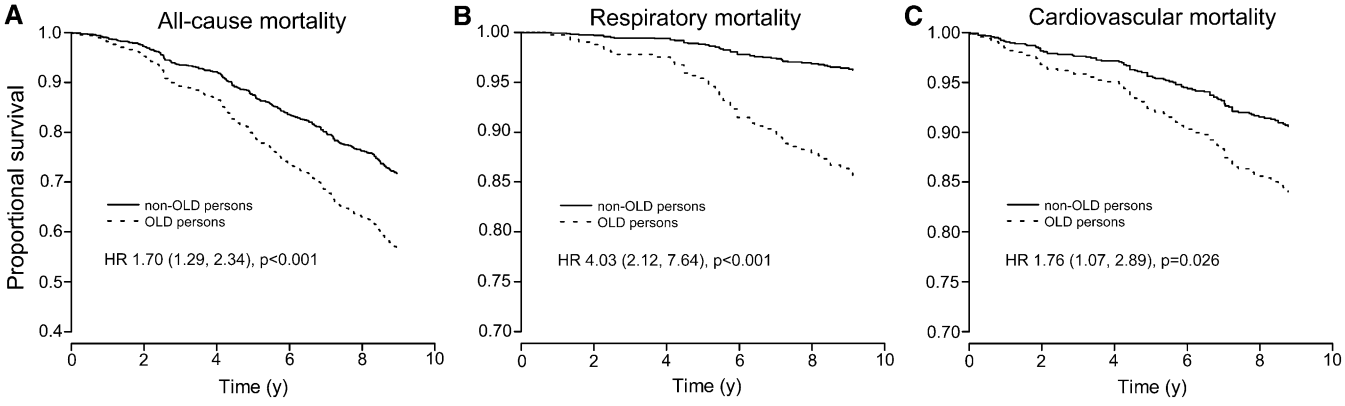

FIGURE 3. All-cause (A), respiratory (B), and cardiovascular (C) mortality of OLD and matched non-OLD participants. Plots are from unadjusted Cox proportional hazards models for n = 972 persons. OLD, obstructive lung disease.

TABLE 4
HRs (95% CIs) of all-cause, cardiovascular, and respiratory mortality according to OLD status and factors accounting for the relation (per 1-SD increase for continuous variables)[1]

	Model 1	Model 2	Model 3	Model 4
All-cause mortality				
OLD status				
Non-OLD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
OLD	1.70 (1.29, 2.34)**	1.72 (1.30, 2.26)**	1.44 (1.05, 1.98)***	1.52 (1.14, 2.03)*
IL-6			1.44 (1.28, 1.61)**	1.41 (1.26, 1.58)**
Adiponectin			1.23 (1.02, 1.48)***	1.18 (0.98, 1.41)****
PAI-1			1.10 (0.96, 1.25)	
VFA			1.13 (0.89, 1.43)	
Hypertension				
No			1 (reference)	
Yes			1.20 (0.86, 1.67)	
Respiratory mortality				
OLD status				
Non-OLD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
OLD	4.03 (2.12, 7.64)**	4.13 (2.19, 7.80)**	3.61 (1.80, 7.25)**	3.66 (1.94, 6.91)**
IL-6			1.50 (1.21, 1.83)**	1.47 (1.18, 1.84)**
Adiponectin			1.21 (0.80, 1.82)	
PAI-1			1.22 (0.82, 1.58)	
VFA			0.96 (0.65, 1.41)	
Hypertension				
No			1 (reference)	
Yes			0.93 (0.48, 1.82)	
Cardiovascular mortality				
OLD status				
Non-OLD	1 (reference)	1 (reference)	1 (reference)	1 (reference)
OLD	1.76 (1.07, 2.89)***	1.75 (1.06, 2.89)***	1.49 (0.85, 2.60)	1.62 (0.96, 2.75)****
IL-6			1.40 (1.14, 1.72)*	1.36 (1.11, 1.66)*
Adiponectin			1.32 (0.99, 1.77)****	
PAI-1			1.12 (0.87, 1.44)	
VFA			1.10 (0.74, 1.64)	
Hypertension				
No			1 (reference)	
Yes			1.24 (0.65, 2.35)	

[1] Analyses were performed by using Cox proportional hazards models. Model 1 was unadjusted. Model 2 was adjusted for age, sex, race, clinic site, BMI, smoking status, and pack-years smoked. Model 3 was adjusted as for model 2 plus adjustment for IL-6, adiponectin, PAI-1, VFA, and hypertension. Model 4 was adjusted as for model 2 plus adjustment for significant predictors of model 3. *$P < 0.01$, **$P < 0.001$, ***$P < 0.05$, ****$P \leq 0.08$. OLD, obstructive lung disease; PAI-1, plasminogen activator inhibitor 1; VFA, visceral fat area.

dietary factors have also been suggested to contribute to systemic inflammation. IL-6 was previously shown to be an independent predictor for mortality in various chronic aging-related diseases such as chronic kidney disease (32), peripheral artery disease (33), and OLD (14). Importantly, IL-6 also has been identified as a predictor of mortality in older populations, after adjustment for

TABLE 5
Primary and underlying causes of OLD deaths and non-OLD deaths[1]

	Primary cause of death		Underlying cause of death	
	OLD (n = 104)	Non-OLD (n = 201)	OLD (n = 104)	Non-OLD (n = 201)
Cardiovascular[2]	32	30	33	34
Respiratory[3]	26	11	15	3
Cancer	1	0	33	40
Gastrointestinal bleeding, renal failure, or sepsis	10	9	2	6
Other[4] or unknown	32	49	16	17

[1] All values are percentages. OLD, obstructive lung disease.
[2] Cardiovascular causes included atherosclerotic cardiovascular disease (definite fatal myocardial infarction, definite fatal coronary heart disease, possible fatal coronary heart disease), cerebrovascular disease, atherosclerotic disease other than coronary or cerebrovascular, and other cardiovascular disease (including valvular heart disease and other).
[3] Respiratory causes included chronic obstructive pulmonary disease, pneumonia, and respiratory failure.
[4] Other causes included dementia, diabetes, and other conditions.

TABLE 6
Dietary intake and physical activity level of OLD and non-OLD participants[1]

	OLD participants	Non-OLD participants	*P* value
Dietary intake[2]			
Energy (kcal/d)	2021 ± 824[3]	1963 ± 791	NS
Protein (g/d)	70.8 ± 29.4	69.1 ± 30.4	NS
Carbohydrate (g/d)	253 ± 109	254 ± 105	NS
Total fat (g/d)	81.5 ± 39.5	74.9 ± 38.7	0.034
Saturated fat (g/d)	24.3 ± 12.6	21.5 ± 11.3	0.003
Cholesterol (mg/d)	250 ± 154	216 ± 141	0.003
trans Fat (g/d)	8.3 ± 6.1	7.4 ± 5.1	0.036
Total dietary fiber (g/d)	16.4 ± 6.9	18.2 ± 8.4	0.007
Vitamin C (mg/d)	129 ± 71	144 ± 79	0.014
Daily glycemic load (glucose scale)	135 ± 62	133 ± 58	NS
Daily glycemic index (glucose scale)	56.7 ± 4.3	56.0 ± 4.7	0.037
Healthy Eating Index	65.0 ± 13.0	67.2 ± 12.9	0.030
Physical activity level[4]			
Total physical activity (kcal · kg^{-1} · wk^{-1})	64.5 (36.4, 98.5)[5]	67.3 (40.5, 109.5)	0.039
Walking briskly ≥90 min/wk (%)	6.6	17.3	<0.001
High-intensity exercise ≥90 min/wk (%)	8.2	17.6	<0.001

[1] Analyses were performed by using random-effects ANOVA. OLD, obstructive lung disease.
[2] Data were available for n = 210 OLD participants and n = 656 non-OLD participants.
[3] Mean ± SD (all such values).
[4] Data were available for n = 243 OLD persons and n = 729 non-OLD persons.
[5] Median; IQR in parentheses (all such values).

chronic diseases (11, 34). Our data strengthen previous studies that identify IL-6 as an important biomarker of mortality risk and extend this by the finding that excessive VF is associated with increased IL-6 in patients with OLD. Future studies are warranted to examine the inflammatory status in VF biopsies from COPD patients and BMI-matched control subjects to further elucidate the contribution of VF to low-grade systemic inflammation in COPD.

Adiponectin is almost exclusively produced by adipocytes and is typically described as an insulin sensitizer with anti-inflammatory properties (35). Paradoxically, increased circulating adiponectin was found to be a strong independent predictor of mortality in a general older population (36) but also in various wasting-associated diseases such as chronic heart failure (CHF) (37, 38), chronic kidney disease (39), respiratory failure (40), and COPD (41). It is noteworthy that adiponectin circulates in high-, middle-, and low-molecular-weight isoforms. These isoforms have different affinities with the adiponectin receptors and therefore their mode of action may differ as well. We measured only total adiponectin in this study, but it might be relevant to explore adiponectin isoforms in future studies because SF and VF release different isoforms (42). Interestingly, whereas we found that VF was strongly negatively associated with plasma adiponectin, persons with OLD—who had increased VF—had elevated adiponectin concentrations. This suggests that other fat depots or even other organ systems are implicated in the elevated adiponectin concentrations in OLD. In a recent study it was found that adiponectin was highly expressed in pulmonary epithelium, and this pulmonary adiponectin expression was strongly increased in emphysematous COPD patients compared with control subjects (43). Adiponectin may play a role in pulmonary inflammation according to a study of ozone exposure in mice (44), although its function in COPD-associated inflammation remains unclear. It has been proposed that elevated adiponectin concentrations increase energy expenditure and induce weight loss through a direct effect on the brain (38, 45), which would be unfavorable in chronic wasting-associated diseases, including COPD. Alternatively, elevated adiponectin concentrations in COPD and CHF (46) may be a sign of adiponectin resistance at the level of skeletal muscle. Lower expression levels of adiponectin receptors in skeletal muscle have been associated with insulin resistance (47), and Van Berendoncks et al (48) recently showed lower adiponectin receptor expression in skeletal muscle biopsies of CHF patients. These data suggest an important cross-talk between adipose tissue and skeletal muscle that warrants further investigation in COPD patients.

Future studies are necessary to identify factors associated with increased VF accumulation in COPD. Poor dietary quality and decreased physical activity levels deserve further attention with respect to body fat distribution in COPD but also point toward the need for more and integrated attention to diet and physical activity in addition to smoking as lifestyle determinants of COPD risk and progression. In addition, hypogonadism has been associated with COPD (49) and with VF accumulation (50). Interestingly, increased VF mass has also been observed in other diseases associated with chronic inflammation, including rheumatoid arthritis (51), Crohn disease (52), and psoriasis (53), which supports a central role for VF in chronic inflammatory diseases.

In conclusion, our study shows increased VF (independent of total fat mass) and a possible role of VF in inflammatory pathways associated with mortality in older persons with OLD.

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